Customer No. 31,834 **Atty. Dkt. No. B-0496 PUS**

REMARKS

Claims 9-15 and 17-25 are pending. Claims 17 and 20 have been amended. Claims 17-24 were previously withdrawn by the Examiner. However, Applicants have amended claims 17 and 20 to make them dependent on claim 9 and request rejoinder of these dependent method claims upon allowance of the product claims. No new matter has been added.

Rejections Under 35 USC §103

Applicants are grateful for the withdrawal of the rejection of Claims 9-15 and 25 under 35 U.S.C. 103(a) for alleged obviousness over Lopresti et al, J. of Clinical Endocrinology and Metabolism, Vol 73, No. 4, 1992, pages 703-709 ("Lopresti") in view of Mol et al ("Mol") and Herfindal et al, In: Clinical Pharmacy and Therapeutics, 1992, pages 289-291 ("Herfindal"), and further in view of Fisher et al US 4,254,095 ("Fisher").

1. **Rejection of Claims 9-10 Under 35 USC §103 Over Lopresti in View of Miura**

Claims 9-10 were rejected for alleged obviousness over Lopresti in View of Miura US 5,116,828 ("Miura"). The Examiner asserts that Lopresti teaches an oral composition comprising T3S in 20 ml 1% albumin solution in distilled water. The Examiner admits that it is unclear if the dosage of Lopresti is within the claimed range, but asserts that "[i]t would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of Lopresti and Miura to manipulate the dosage amount of …T3S… in the composition taught by LoPpresti et al., including applicant's dosage range amount of 5 to 1000 μg, in preparing an oral composition comprising T3S to treat hypothyroidism. One would have been motivated to do so because Miura et al. suggest that the dosage range of thyromimetic drugs is very wide and T3S as taught by LoPresti et al. is also a thyromimetic drug." OA at p. 5.

Applicants respectfully traverse. In order to establish obviousness, it is necessary, *inter alia*, to (i) determine the scope of the prior art and (ii) the differences between the claimed subject matter and that of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Applicants point out that in order to establish a *prima facie* case of obviousness, the examiner must provide a showing that, *inter alia*, the cited prior art references teach or suggest all of the claim limitations and there is some suggestion or motivation to combine the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§2142 and 2143.

Furthermore, a *prima facie* finding of obviousness cannot be established when the "improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1739 (2007). Lastly, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

Applicants respectfully submit that a prima facie case of obviousness has not been established. As an initial matter, contrary to the Examiner's argument (p. 9), Lopresti does not teach an oral composition identical to the instantly claimed composition. Indeed, Lopresti discloses a composition comprising 25 μCi of radio-labeled [I^{125}]T3S. In contrast, the instant invention is directed to oral administration of unradiolabeled T3S. Furthermore, the dosage disclosed in Lopresti is 0.025 to 0.0125 μg, significantly less than the 5-1000 μg of the instant claims.[1]

Most importantly, Lopresti does not teach or suggest that T3S is a thyromimetic drug or that it can be orally administered. Indeed, it repeatedly teaches the opposite: that T3S is an inactive, clinically useless metabolite. See penultimate paragraph of page 704 of Lopresti, before Materials and Methods, wherein it is recited that: "T3S ..... has no detectable biological activity"; further, on page 707, 1st column, last paragraph: "... no clinical evidence of thyroid hormone metabolic effects ..... was noted"; further on page 708, last paragraph: "As T3S is biologically inert .....". See also, Applicants Response to the November 2007 and April 2008 Office Actions (and incorporated herein by reference), which explains in detail why Lopresti teaches that T3S cannot be orally administered as a thyromimetic. For at least these reasons, Lopresti neither teaches nor suggests each element of the claimed invention and, indeed, teaches away from oral administration of T3S as a thyromimetic drug.

Miura does not remedy these deficiencies. As acknowledged by the Examiner Miura is directed to dosages of T3 and T4 and neither teaches nor suggests that T3S is a thyromimemtic or that it can be orally administered for this purpose. Thus, the cited combination of references fails to disclose each and every element of the claimed invention and a prima facie case of obvioiusness has not been established.

[1] Lopresti discloses labeled [^{125} I]T3S with activity ranging from 1000-2000mCi/mg. Thus, the activity per μg is 1000-2000μCi/μg. Lopresti discloses oral dosages of this radiolabeled compound of 25 μCi. This corresponds to 0.025-0.0125 μg, which as explained above, is significantly less than the claimed range.

Additionally, contrary to the Examiner's statement (p 10), the improved properties of the instant oral T3S thyromimetic compositions were not expected based on the teaching of the cited references. Indeed, none of the cited references teaches or suggests that T3S can be administered orally and exert a thyromimetic effect. As explained supra, neither Miura nor Lopresti suggest that oral T3S is useful as a thyromimetic drug and Lopresti teaches the opposite – that T3S is an inactive metabolite with "no clinical evidence of thyroid hormone metabolic effects".

As discussed in more detail below, Santini does not remedy this deficiency as it neither teaches nor suggests that **oral** T3S can exert thyromimetic effects. Moreover, as Lopresti, the only reference to actually investigate oral T3S (albeit radiolabeled T3S), concluded it was not biologically active, was not taken up by the GI system and exerted no thyromimetic effect, one skilled in the art would **not** have expected the superior properties of the presently claimed compounds.

2. **Rejection of Claims 9-15 and 25 Under 35 USC §103 Over Santini et al. in View of Miura**

Claims 9-15 and 25 were rejected for alleged obviousness over Santini et al., Thyromimetic Effects of 3,5,3"-triiodothyronine Sulphate in Hypothyroid Rats, Endocriniology 133(1): 105-110 (1993) ("Santini") in view of Miura. The Examiner states that Santini discloses treatment of thyroidectomised rats with T3S and T3 via intraperitoneal injection. The Examiner admits "[a]lthough Santini et al. teach formulations comprising T3S this reference does not teach compositions comprising T3S in the specific instantly claimed amount of 5 to 1000µ. Further, Santini et al. do not teach the instant claimed combination of T3S and thyroxine." OA, p 7-8. However, the Examiner asserts that it would have been obvious "to manipulate the dosage amount of T3S in the composition taught by Santini et al.,...based on patient parameters such as age, weight and severity of condition." Further, the examiner asserts that it would have been obvious to use Applicants claimed dosage range and thyroxine (T4) in view of Miura's disclosure of T3 and T4 dosage ranges." One would have been motivated to do so because T3S as taught by Santini et al. and T4 as taught by Miura et al. are thyromimetic agents..." Oa at 8.

Applicants respectfully traverse. In order to establish obviousness, it is necessary, *inter alia*, to (i) determine the scope of the prior art and (ii) the differences between the claimed

subject matter and that of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Applicants point out that in order to establish a *prima facie* case of obviousness, the examiner must provide a showing that, *inter alia*, the cited prior art references teach or suggest all of the claim limitations and there is some suggestion or motivation to combine the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§2142 and 2143. Furthermore, a *prima facie* finding of obviousness cannot be established when the "improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1739 (2007). Lastly, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

Applicants respectfully submit that a prima facie case of obviousness has not been established. Santini is directed exclusively to the **intraperitoneal** injection of T3S and the thyromimetic activity discussed resulted only from such intraperitoneal administration. Santini neither teaches nor suggests oral administration. As explained supra, Miura fails to remedy this deficiency. As acknowledged by the Examiner, Miura is directed to dosages of T3 and T4 and neither teaches nor suggests that T3S is a thyromimemtic or that it can be orally administered for this purpose. Thus, the cited combination of references fails to disclose each and every element of the claimed invention and a prima facie case of obvioiusness has not been established.

As explained above, Lopresti, the only reference to address oral T3S (albeit radiolabled T3S) taught that T3S was an inactive metabolite which was not absorbed by the GI system upon oral administration. Thus, one skilled in the art believing T3S exerted possible thyromimetic activity based on Santini and aware of Lopresti, as well as the highly polar nature of T3S, would have **no** expectation that T3S would be properly absorbed upon oral ingestion so as to act as an oral thyromimetic drug. Thus, the combination of Santini with any of the cited references would teach the skilled artisan that only by **intraperitoneal** administration could one expect any thyromimetic activity from T3S.

In sum, as Lopresti, the only cited reference which actually investigated the thyromimetic activity and metabolism of **oral** T3S (albeit radiolabeled T3S), showed it would not be absorbed upon oral administration, the claimed compositions must be regarded as unpredictable and unexpected over the aforementioned prior art references, either taken alone or in combination. Furthermore, as none of the cited references teaches or suggests the oral

administration of T3S, the dosage limitations recited in the claims cannot be deemed to be mere dose optimization. Indeed, the utility of and unexpected advantages associated with oral administration of T3S were established only with the instant invention, as shown by the Experimental Data submitted with Applicants 1/29/08 Amendment and Response, which is incorporated herein by reference.

CONCLUSION

In view of the preceding remarks, it is believed that claims 9-15 and 25 are in condition for allowance. Applicants request rejoinder of claims 17-24.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment. However, if any fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

Dated: May 19, 2009

M. Caragh Noone, Reg. No. 37,197
Bracco Research USA Inc.
305 College Road East
Princeton, NJ 08540
Tel: (609) 514-2454
Fax: (609) 514-2446